IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Julie Straub, David Altreuter, Howard Bernstein, Donald E. Chickering, III, Sarwat Khattak, and Greg Randall		
Serial No.:	10/053,929	Art Unit:	1618
Filed:	January 22, 2002	Examiner:	Blessing M. Fubara

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

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Commissioner for Patents
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REPLY BRIEF TO EXAMINER'S ANSWER

Sir:

This is a reply brief to the Examiner's Answer mailed October 18, 2007, in the above-referenced application. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $1,030.00, the fee for the Request for Oral Hearing for a large entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue on appeal is:

(a) whether claims 16-21 and 34 are obvious under 35 U.S.C. § 103(a) over U.S. Patent Application Publication No. 2001/0018072 to Unger ("Unger").

(7) ARGUMENT

Appellants affirm all of the arguments made in the Appeal Brief.

(i) Rejection Under 35 U.S.C. § 103

Unger does not disclose or suggest at least elements (b), (c), and (d) of claim 16

Unger does not disclose forming a drug solution

In the Examiner's Answer, the Examiner alleges that Unger discloses steps (b), (c), and (d) of the claimed method since Unger discloses a method of making a porous matrix by combining surfactant, bioactive agent or therapeutic agent, together with a solvent and optionally a gas or gaseous precursor (*see* page 4, paragraph (a), lines 12-18 of the Examiner's Answer). Applicants respectfully disagree. Unger describes a method for preparing a solid porous matrix (abstract). The matrix is prepared by combining a surfactant and a therapeutic, together with a solvent, to form an emulsion containing random aggregates of the surfactant and the therapeutic, and processing the emulsion to form the matrix (abstract). The solvent is a **suspending** medium for associating the surfactant with the therapeutic in the preparation of the solid matrix. Unger discloses that the therapeutic agent is marginally soluble in the solvent. In contrast, the claimed methods require that the active agent be dissolved in a volatile solvent to form a drug solution.

A suspension is not the same as a solution. Unger teaches away from the claimed methods. Accordingly, claims 16-21 and 34 are not obvious over Unger.

Unger does not disclose or suggest adding a volatile solid pore forming agent to the drug solution and then removing the volatile solid pore forming agent

Unger describes the use of gases, or gaseous precursors which generate gases, which are entrapped within the matrix (page 20, paragraph 0160 to page 22, paragraph 0175). Unger alleges that the gas is entrapped within preformed voids and provides the solid porous matrix with enhanced reflectivity. Paragraphs 0184-190 cited by the Examiner do not disclose or suggest the use of a volatile solid pore forming agent to form a porous matrix. Paragraph 0184 discloses that a solid porous matrix containing a surfactant and a therapeutic is prepared by combining a solvent, a surfactant, and a therapeutic to form an emulsion in the form of a random aggregate. In the case of spray drying, the emulsion or colloidal suspension is placed into association with a blowing agent, such as methylene chloride. Methylene chloride is a volatile organic solvent; it is not a volatile solid pore forming agent as required by the claims. The gaseous precursors described in Unger are used to generate a gas which is trapped within the matrix, not as "pore forming agents" which are removed from the matrix as required by the claims. This is supported by the Examiner's statements in the Examiner's Answer. The Examiner states that the method disclosed in Unger optionally uses a gas or gaseous precursor (*see* page 4, paragraph (a), line 18 of the Examiner's Answer). The fact that this component is optional is evidence that the gas or gaseous precursor is not used as a pore forming agent.

Unger also describes the use of gaseous precursors as a solvent in the preparation of the solid matrix (page 20, paragraph 0161). In contrast, the claimed method requires the addition of a volatile solid pore forming agent, which is removed and upon removal, forms a porous matrix. While Unger discloses that the gaseous precursor may be added to the surfactant and the therapeutic and removed during processing (page 20, paragraph 0161), this disclosure is specifically in regard to gaseous precursors that are used as a solvent in the preparation of a solid porous matrix. None of Unger's examples describe adding a volatile solid pore forming agent to a drug solution to form a suspension, emulsion, or second solution and then removing the volatile solid pore forming agent to form a porous matrix.

In addition to the arguments provided above with respect to claim 16 and its dependent claims, claims 19 and 20 are non-obvious because Unger does not disclose or suggest the use of volatile salts as pore forming agents. Unger does not disclose or suggest the use of volatile salts as solid pore forming agents, let alone the specific salts listed in claim 20. Accordingly, claims 16-21 and 34 are not obvious over Unger.

Unger does not disclose compositions containing an excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth

Unger discloses the use of a stabilizing material. However, Unger's stabilizing material is used to stabilize the vesicle containing the active agent and/or to prevent escape of the gases, gaseous precursors, or bioactive agents. Unger does not disclose or suggest the use of at least one excipient which enhances the dissolution rate of the drug, stabilizes the drug in an

amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth as required by claim 16.

The Examiner points to paragraph 0019 in Unger which defines a surfactant or surface active agent as a substance that alters energy relationships at interfaces, such as for example, synthetic organic compounds displaying surface activity including, *inter alia*, wetting agents, detergents, penetrants, spreaders, dispersing agents, and foaming agents. The Examiner alleges that claim 18 defines classes of excipients that overlap with Unger's definition of surfactant. Claim 18 depends from claim 16. The excipients listed in claim 18 are a subset of excipients which must have the characteristics defined in claim 16. Unger does not teach one of ordinary skill in the art to select excipients having the properties defined in claim 16. In fact, Unger is silent regarding excipients that enhance the dissolution rate of the drug, stabilize the drug in an amorphous form by preventing crystallization, or stabilize the drug in crystalline form by inhibiting crystal growth. Accordingly, claims 16-21 and 34 are not obvious over Unger.

Unger's Example 1 does not meet the limitations of Claim 16

In the Examiner's Answer, the Examiner concedes that Example 1 does not meet the limitations of claim 16, and it is for this reason that the rejection over Unger is for obviousness and not anticipation (*see* page 6, paragraph (f) of the Examiner's Answer). However, in the Final Office Action mailed December 8, 2006, the Examiner alleges that prophetic Example 1 in Unger describes steps (a), (b), and (d) of claim 16 and uses this allegation as the basis for the obviousness rejection (*see* the Final Office Action mailed on December 8, 2006). This allegation is incorrect. Example 1 describes the encapsulation of dexamethasone in PEG Telomer B, which

is a surfactant. Unger predicts that 20% of the PEG-Telomer B aggregate complex is dexamethasone. PEG Telomer B is not a volatile pore forming agent. PEG Telomer B is not removed from the mixture. Further, even if one could argue that PEG Telomer B is a volatile pore forming agent, it is not a volatile solid pore forming agent. PEG Telomer B is a liquid having a boiling point of 200°C (*see* the enclosed Material Safety Data Sheet for PEG Telomer B, originally submitted with Response filed June 25, 2007). Example 1 does not disclose the addition of a volatile solid pore forming agent to a drug solution. Further, Example 1 does not disclose removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient as required by claim 16. Accordingly, claims 16-21 and 34 are not obvious over Unger.

Unger does not disclose or suggest microparticles with the properties required by claim 16

Claim 16 specifies the properties of the compositions formed using the claimed method. Unger does not disclose or suggest that the microparticles formed using its process have the properties specified by claim 16. The Examiner alleges that the product formed by Unger and the claimed method have the same constituents, and thus it follows that the composition of the product formed by the claimed method and that formed by the Unger method are the same (*see* page 7, paragraph (i) of the Examiner's Answer). The Examiner is incorrect. Applicants have clearly shown that the claimed method is substantially different from the method described in Unger. Unger does not disclose preparing a drug solution. Unger does not disclose adding a volatile solid pore forming agent to the drug solution to form an emulsion, suspension, or second

solution. Unger does not disclose incorporating at least once excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth. Unger does not disclose removing the volatile solvent and pore forming agent to yield a porous matrix. Thus, the Examiner's allegation that the composition disclosed in Unger inherently have the same properties as those defined in the claimed method is without merit. Accordingly, claims 16-21 and 34 are not obvious over Unger.

Evaluating evidence of secondary considerations

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, etc.

The claims are drawn to methods of making pharmaceutical compositions. These methods are particularly useful for formulating pharmaceutical compositions containing drugs having low solubility. As discussed in the specification, the bioavailability of a drug can be limited by poor dissolution of the drug into aqueous bodily fluids following administration (page 1, lines 17-18). This rate- limiting step can be critical to rapidly attaining therapeutically effective drug levels (page 1, lines 18-20).

Traditional approaches to parenteral delivery of poorly soluble drugs include using large volumes of aqueous diluents, solubilizing agents, detergents, non-aqueous solvents, or non-physiological pH solutions (page 1, lines 20-23). These formulations, however, can increase the systemic toxicity of the drug composition or damage tissues at the site of administration (page 1, lines 23-25).

Other approaches disclosed in the prior art have focused on the physical form of the drug itself. For example, drugs have been prepared in nanoparticulate form. Nanoparticles, however, can be difficult to produce and maintain in a stable form due to their tendency to flocculate or agglomerate, particularly in the absence of surface modifying agents absorbed or coated onto the particles (page 1, line 31 to page 2, line 3). Further, techniques used for nanonization are typically undesirable due to: (1) the time it takes to process a single batch (e.g., several days); (2) scale up of such techniques can be difficult and costly; and (3) the process can be difficult to conduct aseptically (page 2, lines 3-8). Thus, at the time of the priority application, there existed an unmet need for formulations containing poorly soluble drugs which exhibit increased dissolution of the drug. The claimed methods are quite versatile and are generally useful for increasing the dissolution rates of drugs.

Application of the *Graham* factors demonstrates that one or ordinary skill in the art would not have been motivated to modify Unger to arrive at the claimed methods. Unger is concerned with targeted drug delivery, not formulating poorly soluble drugs to have enhanced dissolution *in vivo*. Unger describes the use of stabilizing materials to stabilize the vesicle containing the active agent, not to enhance dissolution or prevent crystallization of the drug as required by claim 16. Unger does not disclose or suggest steps (b), (c), and (d) of claim 16. Unger does not disclose or suggest microparticles having the properties defined in claim 16. One of ordinary skill in the art would not be motivated to modify Unger to arrive at the claimed methods. Therefore claims 16-21 and 34 are not obvious in view of Unger.

(8) SUMMARY AND CONCLUSION

Unger does not disclose or suggest a method for making microparticles comprising forming a drug solution, adding a volatile solid pore forming agent to the drug solution to form a suspension, emulsion, or second solution, and removing the pore forming agent to form a porous matrix as required by claim 16. Unger does not disclose or suggest that the microparticles formed using its process have the properties required by claim 16. Unger does not disclose or suggest every element of the claims. Further, the Examiner has provided no reason why one of ordinary skill in the art would be motivated to modify Unger to arrive at the claimed methods. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness.

For the foregoing reasons, Appellant submits that claims 16-21 and 34 are patentable.

Respectfully submitted,

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